DEVELOPMENT OF POLYSACCHARIDE-BASED NANOCOMPOSITE HYDROGELS AS DRUG DELIVERY SYSTEMS FOR ANTICANCER DRUGS

FINAL SYNOPSIS

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Introduction

Polysaccharides are long chains of monosaccharides connected through glycosidic linkages. They occur naturally in living organisms and possess various functions, such as energy storage,[1] structural support and identifiers for cellular communications.[2,3] For instance, starch is the primary energy source component in plants, while glycogen is used for energy storage in animals. Cellulose found in plant cell walls provides structural support and firmness. Chitin in the exoskeleton of arthropods and the cell wall of fungi provides strength and protection. Further, polysaccharides exhibit diverse properties due to variations in monosaccharide units, arrangement and bonding patterns, which make them useful materials for various applications.

Polysaccharides offer numerous benefits in drug delivery applications, making them valuable components in developing practical and safe drug delivery systems. They are highly regarded for their ability to improve therapeutic efficacy in various drug delivery systems.[4] One of the key strengths lies in their natural origin, reducing the risk of adverse effects when used as drug delivery systems.[5] Moreover, polysaccharides can be ingeniously engineered to achieve controlled drug release, making them valuable for medications requiring sustained therapeutic effects.[6,7] By attaching functionalized materials to polysaccharide-based systems, drugs can be precisely delivered to specific sites, reducing off-target effects and optimizing therapeutic efficacy.[8] Additionally, polysaccharides in drug delivery systems can enhance the solubility of hydrophobic drugs, a common challenge in pharmaceutical formulations. Polysaccharides protect labile therapeutic agents, shielding them from enzymatic degradation or environmental factors, such as pH and temperature, until they reach the intended delivery sites.[9] Being biodegradable in the gastrointestinal tract is another significant feature of polysaccharides, facilitating the release of the incorporated drug. Polysaccharides can naturally degrade into non-toxic byproducts.[10] Therefore, using polysaccharides in advancing drug delivery systems is a

promising approach for improving drug efficacy and safety, contributing to healthcare applications.

Polysaccharide-based nanocomposite hydrogels are cutting-edge classes of materials with diverse applications in biomedicine, drug delivery and tissue engineering.[11] These polymer materials commonly possess promising structural morphologies suitable for drug entrapment, providing a reservoir for controlled and sustained release over a prolonged period. By adjusting the parameters, such as crosslinking density, polymer compositions and concentration of nanoparticles, the drug release kinetics can be tailored to match the desired properties, reducing off-target effects and improving therapeutic outcomes. Further, these polymer matrix materials are suitable for combination therapy strategy, where multiple therapeutic agents are incorporated to overcome drug resistance and achieve synergistic effects.[12] Generally, polysaccharide-based nanocomposite hydrogels are promising polymer materials for advancing the field of drug delivery, providing innovative results for personalized and effective treatment of various diseases. They offer exciting prospects in cancer therapy, increase specificity and reduce toxicity-related concerns,[13] as supported by various recent studies.[14–16]

Nanocomposite hydrogels containing magnesium oxide, xanthan gum and acrylic acid;[17] iron oxide, montmorillonite and alginate;[14] and carboxymethylcellulose, chitosan, β-cyclodextrin and iron oxide nanoparticles[18] have been reported for delivery of the drug methotrexate.

The nanocomposite hydrogels made from guar gum, polyacrylamidoglycolic acid and silver nanoparticles (SNPs);[19] poly(acrylamide-*co*-acrylamidoglycolic acid), guar gum and SNPs;[20] agarose, chitosan and γ-alumina nanoparticles[21] and polyacrylic acid, chitosan and iron oxide[22] have been developed and evaluated for delivery of 5-fluorouracil (5-FU).

The matrices comprising of zinc oxide nanoparticles, starch and carboxymethylcellulose crosslinked with iron (III) ions;[23] chitosan and iron oxide crosslinked with tripolyphosphate;[24] poly(N-isopropyl acrylamide), alginate and graphene-iron oxide,[25] cellulose nanocrystals,

poly(acrylic acid) and magnesium oxide;[26] and oxidized starch, poly(vinyl alcohol) and copper (II) oxide nanoparticles[27] have been developed and reported for delivery of doxorubicin (DOX).

The nanocomposite polymer matrices composed of montmorillonite, kappa-carrageenan and chitosan were studied for the delivery of sunitinib.[28] Similarly, a multi-sensitive nanocomposite prepared from alginate and gold nanoparticles has been made and evaluated for delivery of cisplatin (CPT).[29]

The nanocomposite polymer materials consisting of chitosan and SNPs;[30] carboxymethylcellulose, starch and graphene oxide; starch, poly(acrylic acid) and titanium dioxide[16] have been developed and studied for delivery of curcumin (CUR).

The nanocomposite containing carboxymethylcellulose, poly(acrylic acid), modified starch and iron oxide has been designed[31] for the co-delivery of 5-FU and DOX. Further, chitosan/agarose chitosan[32] and chitosan/reduced graphene oxide nanocomposites[33] have been reported for co-delivery of 5-FU and CUR.

Objectives of the present study

i) To prepare polysaccharide-based nanocomposite hydrogels using polysaccharides as the main components, and a few synthetic monomers and SNPs for modification.
ii) To characterize the polymer matrix materials using relevant advanced analytical techniques.
iii) To study the swelling behavior of the polymer matrix materials.
iv) To estimate the drug loading and entrapment efficiency of the polymer matrix materials for a few anticancer drugs.
v) To establish the drug release profiles of the polymer matrix materials.
vi) To study drug release kinetics and mechanism of the polymer matrix materials.
vii) To assess the cytotoxicity of the polymer matrix materials.

Thus, the survey of the literature on systems for delivery of drugs indicates that polysaccharide-based nanocomposite hydrogels present dynamic opportunities for delivering anticancer drugs. Despite the promising properties of polysaccharides for delivering anticancer drugs, many polysaccharides are not widely studied in the form of nanocomposites. Additionally, the delivery of anticancer drugs in combined form is still at the embryonic stage; hence, it deserves further study. Therefore, the development of polysaccharide-based nanocomposite hydrogels for the delivery of anticancer drugs was planned in the present work. Different polysaccharides, namely, dextran (Dex), pectin (Pec), locust bean gum (LBG) and gum arabic (GA) were modified by grafting with small amounts of synthetic monomers, namely 4-acryloylmorpholine (AcM) and 2-acrylamido-2-methyl-1-propanesulphonic acid (AMPS) and appropriate amount of SNPs were employed for further modification. The selected polysaccharides are widely available, soluble in water, pH-responsive, biodegradable, non-toxic, easy to modify but are not widely studied in the form of nanocomposite hydrogels. Additionally, the selected monomers are less toxic, soluble in water, pH-responsive and compatible with many polysaccharides. In particular, AcM enables fast gelation and facilitates the entrapment of the hydrophobic drugs due to the presence of hydrophobic morpholine moieties. Similarly, AMPS enhances the hydrophilicity of the nanocomposite, promising for the entrapment and release of hydrophilic drugs. The polymer matrices were made using the microwave (MW) irradiation technique. During preparation, ammonium peroxodisulphate (APS) was used as the initiator because it is soluble in water, highly reactive, selective and can be decomposed at low energy. The N, N'-methylenebisacrylamide (MBA) was used as a crosslinking agent because of its good compatibility with many polymers, soluble in water and easy to remove during purification. SNPs were formed and incorporated in polymer networks via an *in situ* approach during the preparation of polymer matrix materials. The choice of the SNPs was attributed to their wide compatibility with healthy cells, ability to be formed in an aqueous medium and potential to enhance the functionalities of the polymer matrices for drug delivery applications. Along with

the nanocomposites, the corresponding pristine hydrogels (without nanoparticles) were also prepared to evaluate the influence of nanoparticles on the efficiency of the matrices for drug delivery.

The prepared matrices were characterized by Fourier transform infrared (FT-IR) spectroscopy, field emission scanning electron microscopy (FE-SEM), energy dispersion X-ray spectroscopy (EDS), high-resolution transmission electron microscopy (HR-TEM), X-ray diffraction (XRD) and thermogravimetric analysis (TGA) techniques. The swelling behavior of the prepared polymer materials was studied in buffer solutions with different pH levels. The efficiency of the matrices to load, encapsulate and release four anticancer drugs, namely 5-FU, CUR, CPT and DOX, in single and combined forms, was investigated at 37 °C in buffer solutions of different pH, mimicking gastrointestinal conditions using UV-Vis spectroscopy. The kinetic and mechanistic aspects of the drug release were determined using relevant kinetic models. Further, cytotoxicity of the prepared matrices was studied on intestinal epithelium normal cells (IEC-6) and breast normal cells (MCF-10A) using the MTT assay to evaluate the cytocompatibility of the matrices for drug delivery applications. The work presented in the thesis is divided into the following chapters.

Chapter-1: Introduction

Chapter-2: Experimental section

Chapter-3: Dextran-based silver nanocomposite hydrogels: Preparation, characterization and drug delivery applications.

3A: Preparation of dextran-*graft*-poly(4-acryloylmorpholine) silver nanocomposite hydrogel for oral delivery of curcumin.

3B: Preparation of dextran-*graft*-poly(4-acryloylmorpholine-*co*-2-acrylamido-2-methyl-1-propanesulphonic acid) silver nanocomposite hydrogel for oral co-delivery of 5-fluorouracil and cisplatin.

Chapter-4: Pectin-based silver nanocomposite hydrogels: Preparation, characterization and drug delivery applications.

4A: Preparation of pectin-*graft*-poly(4-acryloylmorpholine) silver nanocomposite hydrogel for oral co-delivery of 5-fluorouracil and curcumin.

4B: Preparation of pectin-*graft*-poly(4-acryloylmorpholine-*co*-2-acrylamido-2-methyl-1-propane sulphonic acid) silver nanocomposite hydrogel for oral co-delivery of 5-fluorouracil and doxorubicin.

Chapter-5: Locust bean gum-based silver nanocomposite hydrogels: Preparation, characterization and drug delivery applications.

5A: Preparation of locust bean gum-*graft*-poly(4-acryloylmorpholine) silver nanocomposite hydrogel for oral delivery of 5-fluorouracil.

5B: Preparation of locust bean gum-*graft*-poly(4-acryloylmorpholine-*co*-2-acrylamido-2-methyl-1-propane sulphonic acid) silver nanocomposite hydrogel for oral co-delivery of cisplatin and doxorubicin.

Chapter-6: Gum arabic-based silver nanocomposite hydrogels: Preparation, characterization and drug delivery applications.

6A: Preparation of gum arabic-*graft*-poly(4-acryloylmorpholine) silver nanocomposite hydrogel for oral co-delivery of curcumin and cisplatin.

6B: Preparation of gum arabic-*graft*-poly(4-acryloylmorpholine-*co*-2-acrylamido-2-methyl-1-propane sulphonic acid) silver nanocomposite hydrogel for oral co-delivery of curcumin and doxorubicin.

Summary and Conclusions

References

Brief overviews of the chapters

Chapter-1: Introduction

This chapter provides an introduction to polysaccharide hydrogels and their nanocomposites. A comprehensive literature on polysaccharide-based nanocomposite hydrogels as drug delivery systems has been presented with a main focus on the oral delivery of anticancer drugs. Additionally, special emphasis has been placed on Dex, Pec, LBG and GA-based nanocomposite hydrogels and their application in oral drug delivery. The objectives of the study are also presented at the end of the chapter.

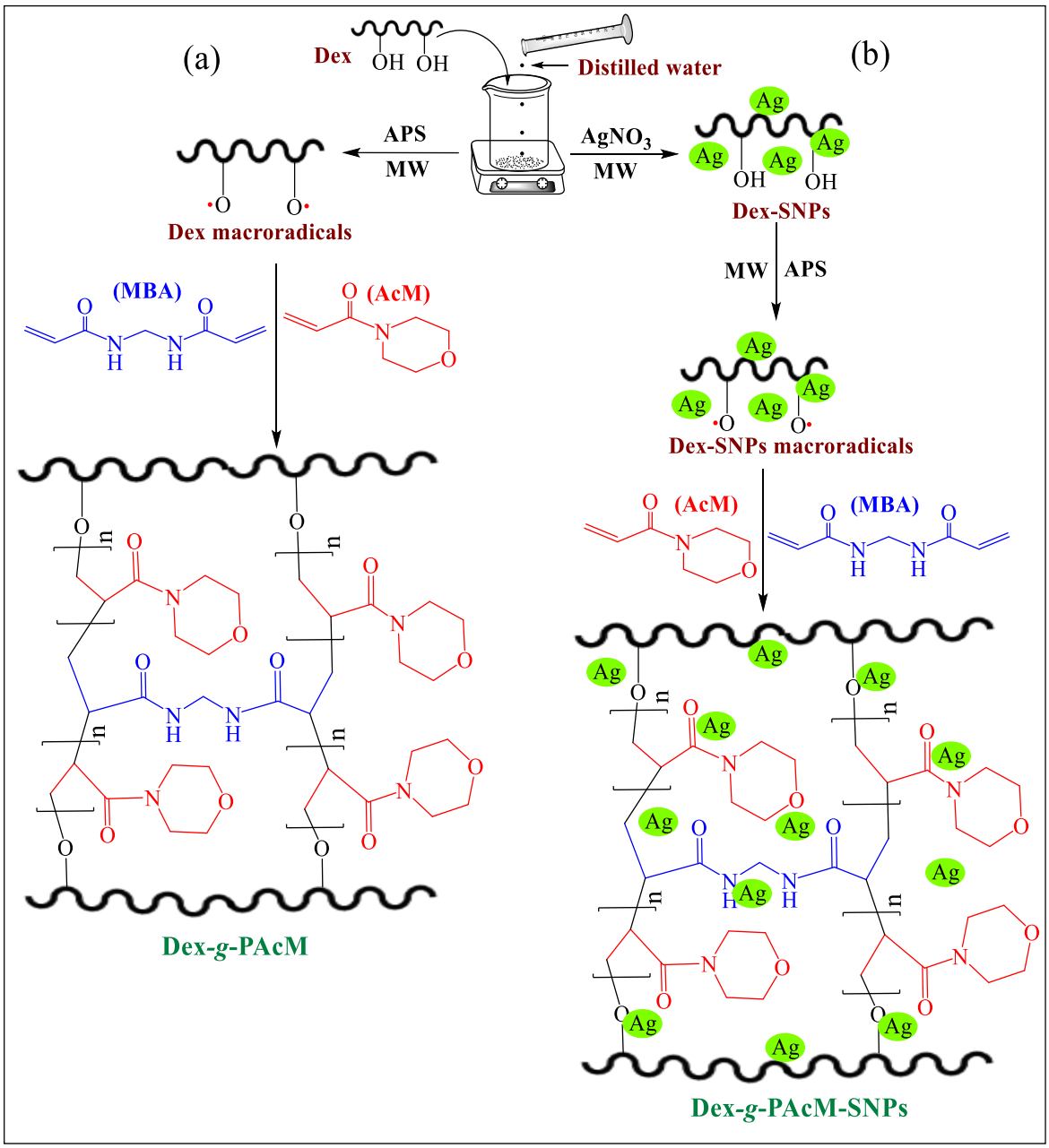
Chapter-2: Experimental section

This chapter addresses the materials used during the study, methods employed for the preparation of the polymer matrices, instruments employed for characterization and analyses of the prepared polymer matrices, methods adopted for the drug release study and the theoretical models used to evaluate the experimental data.

Chapter-3: Dextran-based silver nanocomposite hydrogels: Preparation, characterization and drug delivery applications

This chapter focuses on the preparation of Dex-based nanocomposite hydrogels along with the corresponding pristine gels, characterization and evaluation of their efficiencies for the oral delivery of anticancer drugs for cancer treatment. The chapter is divided into two sections.

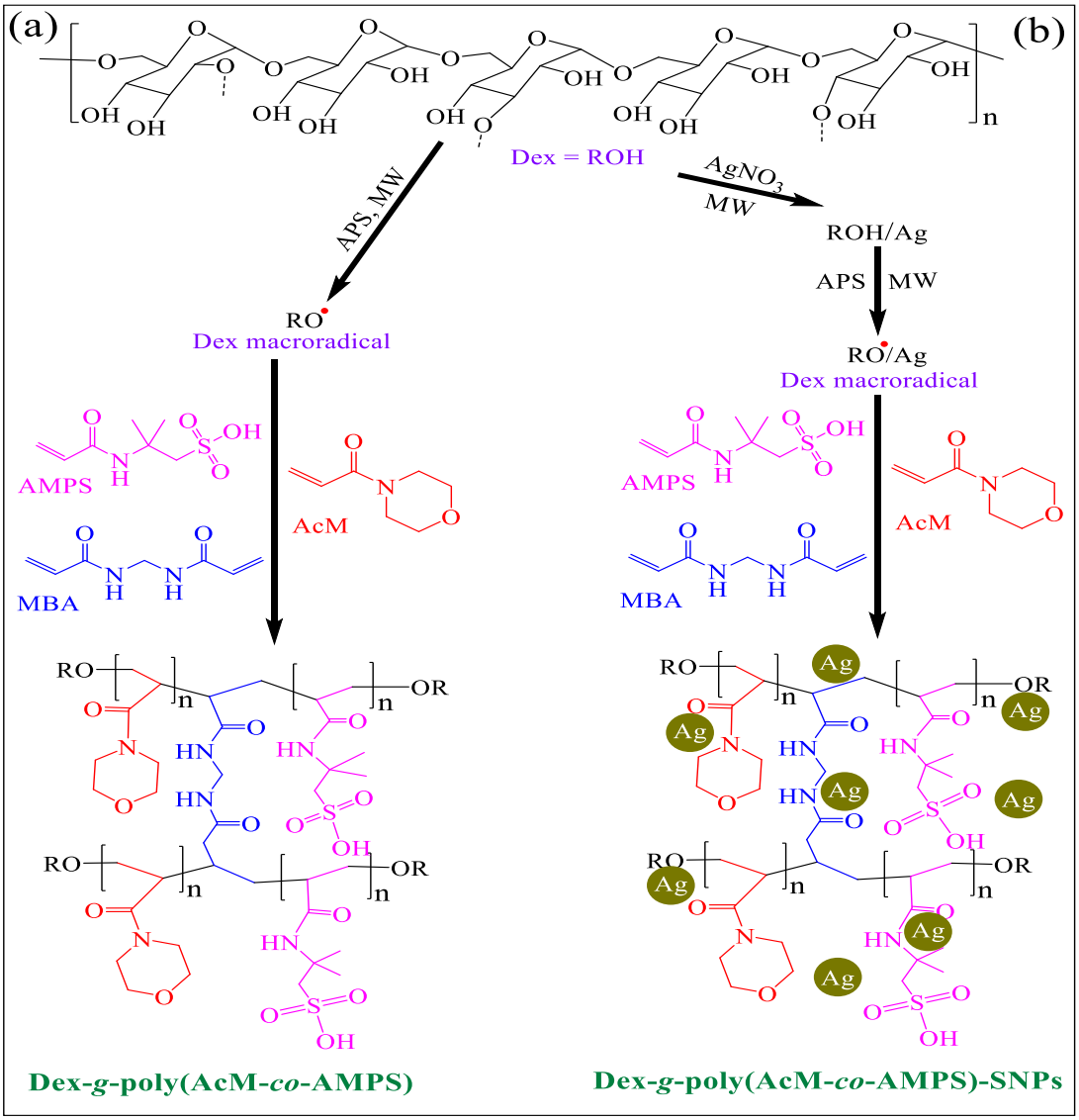
In **Section A** of this chapter, the preparation and characterization of the nanocomposite hydrogel containing Dex, AcM and SNPs, its corresponding pristine hydrogel (**Scheme 1**) and their applicability for the oral delivery of CUR have been discussed.



Scheme 1: Mechanism of formation of the (a) pristine gel Dex-*g*-PAcM and (b) nanocomposite Dex-*g*-PAcM-SNPs

The matrices showed higher swelling and drug release at pH 1.2 (simulated gastric fluid (SGF)) than at pH 7.4 (simulated intestinal fluid (SIF)). The drug release data obtained at pH 1.2 was further evaluated for release kinetics and mechanism, which were found to best fit with the first-order kinetic and Higuchi square root models. The transport of the incorporated drug from the polymer matrices to the dissolution medium adhered to a non-Fickian diffusion mechanism. The cytotoxicity study of the MCF-10A cells demonstrated the cytocompatibility of the developed nanocomposite.

In **Section B** of this chapter, the preparation and characterization of the nanocomposite containing Dex, AcM, AMPS and SNPs as well as the corresponding pristine hydrogel (**Scheme 2**) and their applicabilities for the oral co-delivery of 5-FU and CPT have been discussed.



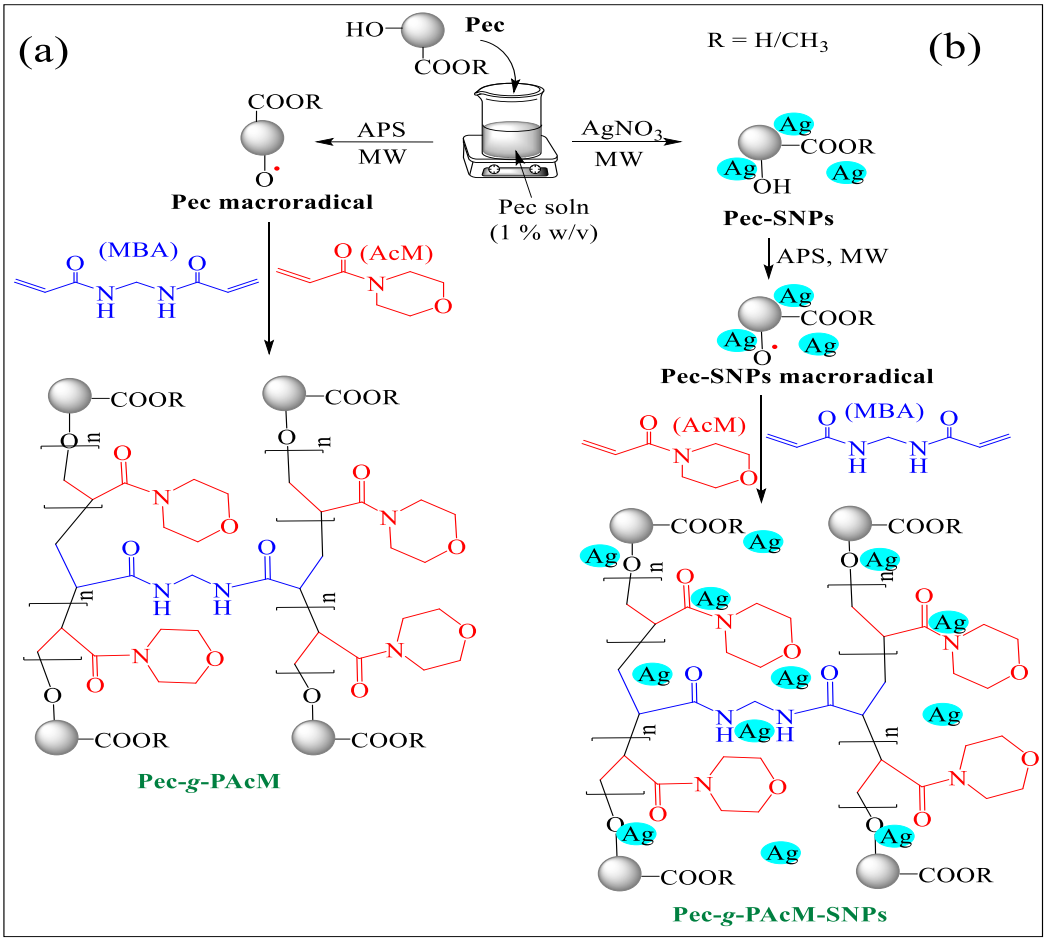
Scheme 2: Mechanism of formation of the (a) pristine gel Dex-*g*-poly(AcM-*co*-AMPS) and (b) nanocomposite Dex-*g*-poly(AcM-*co*-AMPS)-SNPs

The matrices showed higher swelling and high drug release at pH 7.4 (SIF) than at pH 1.2 (SGF). The drug release data obtained at pH 7.4 was observed to obey the first-order kinetic and Higuchi square root models. The transport of the two incorporated drugs from the polymer matrices to the dissolution medium corresponded to a non-Fickian diffusion mechanism. The cytotoxicity study on MCF-10A cells indicated remarkable cell viability, suggesting the cytocompatibility of the developed nanocomposite.

Chapter-4: Pectin-based silver nanocomposite hydrogels: Preparation, characterization and drug delivery applications

This chapter focuses on the preparation of Pec-based nanocomposite hydrogels along with the corresponding pristine gels, characterization and evaluation of their efficiencies for the oral delivery of anticancer drugs for cancer treatment. The chapter is divided into two sections.

In **Section A** of this chapter, the preparation and characterization of the nanocomposite hydrogel containing Pec, AcM and SNPs, as well as corresponding pristine hydrogel (**Scheme 3**) and their utilities for the oral co-delivery of 5-FU and CUR have been discussed.

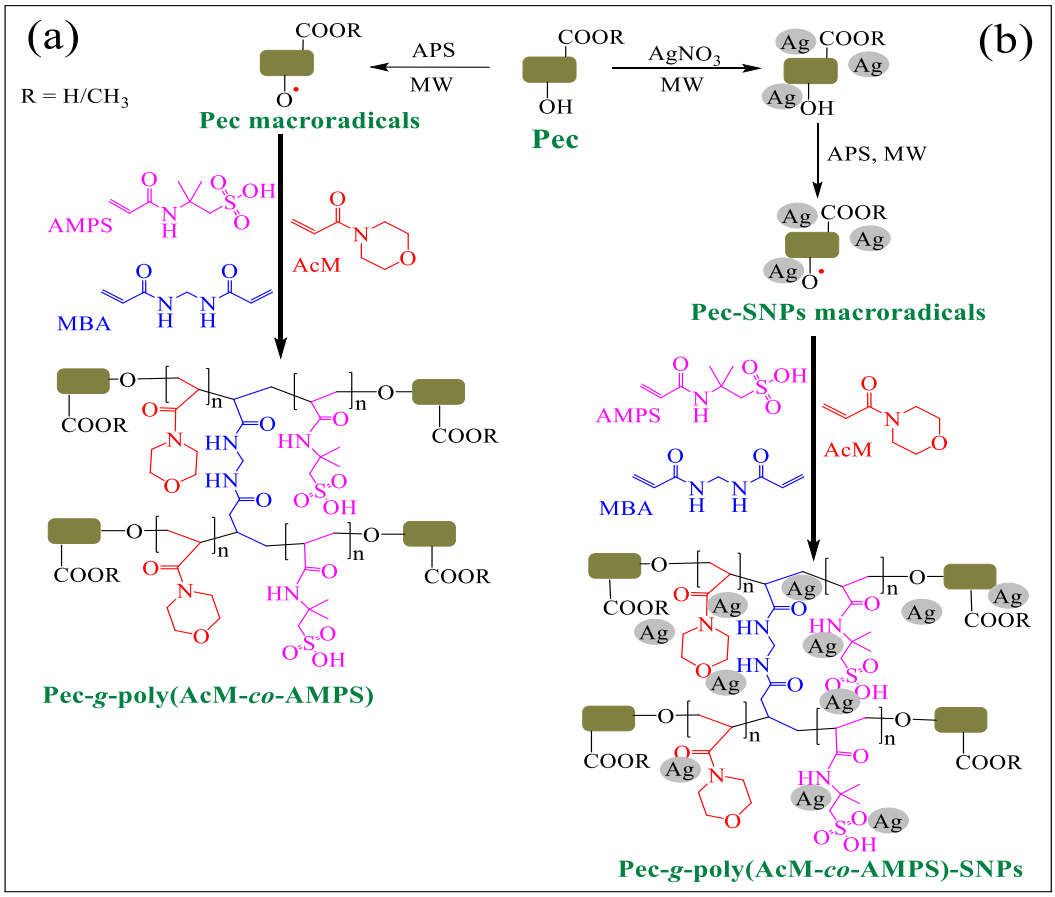


Scheme 3: Mechanism of formation of the (a) pristine gel Pec-*g*-PAcM and (b) nanocomposite Pec-*g*-PAcM-SNPs

The polymer matrices showed higher swelling and drug release at pH 7.4 (SIF) than at pH 1.2 (SGF). The drug release data obtained at pH 7.4 was further investigated in terms of release kinetics and mechanism. It was observed that the drug release process followed the first-order kinetic and Higuchi square root models. The transport of the incorporated drugs form the

polymer matrices to the dissolution medium followed a Fickian diffusion for 5-FU and non-Fickian diffusion for CUR. The cell viability study showed that the developed nanocomposite is cytocompatible, as confirmed on the MCF-10A cells.

In **Section B** of this chapter, the preparation and characterization of the nanocomposite hydrogel containing Dex, AcM, AMPS and SNPs as well as the corresponding pristine hydrogel (**Scheme 4**) and their applicabilities for the oral co-delivery of 5-FU and DOX have been discussed.



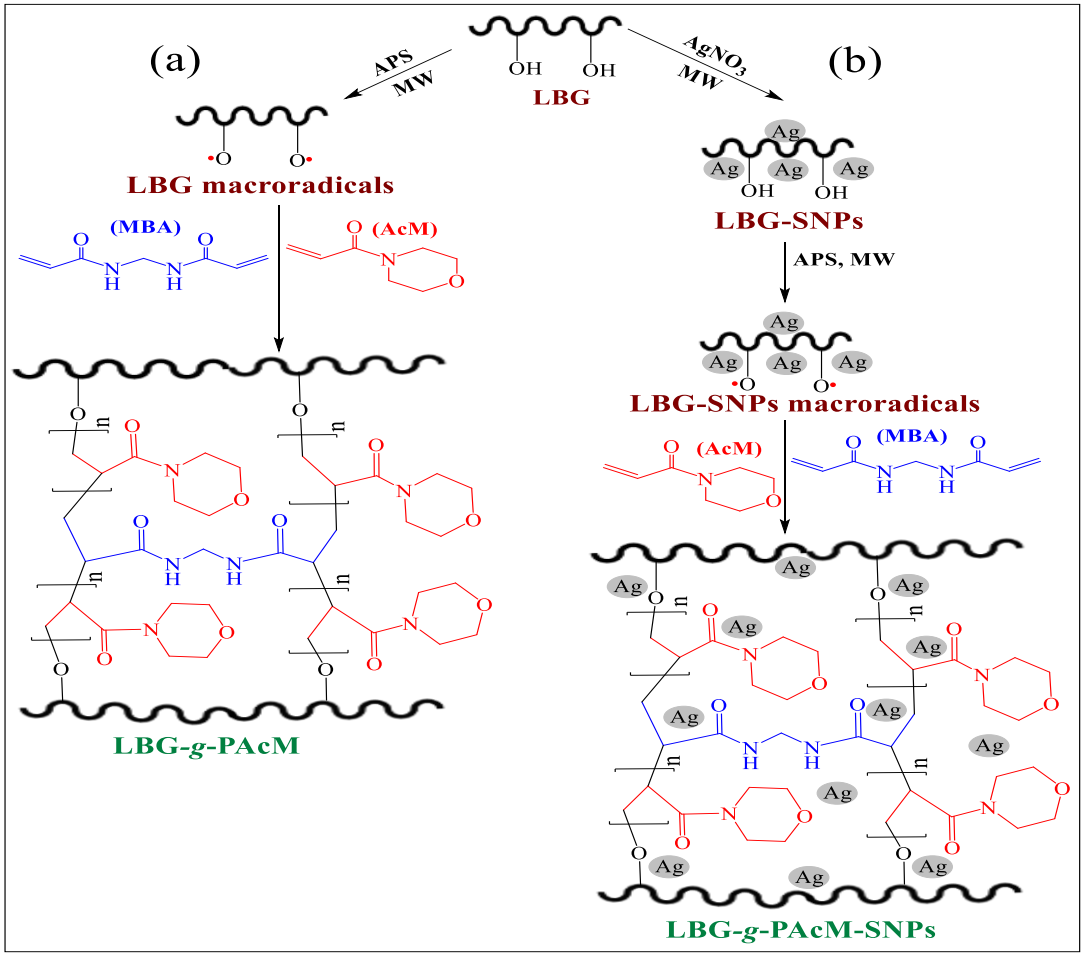
Scheme 4: Mechanism of formation of (a) pristine gel Pec-*g*-poly(AcM-*co*-AMPS) and (b) nanocomposite Pec-*g*-poly(AcM-*co*-AMPS)-SNPs

The matrices showed higher swelling and drug release at pH 7.4 (SIF) than at pH 1.2 (SGF). The drug release process at pH 7.4 was best fitted to the first-order kinetic and Korsmeyer Peppas models. The transport of two incorporated drugs from the polymer matrices to the dissolution medium adhered to a Fickian diffusion. The cytotoxicity study showed that the prepared nanocomposite matrix is cytocompatible, promising its employability as a matrix material for oral co-delivery of 5-FU and DOX, as revealed by high viability of MCF-10A cells.

Chapter-5: Locust bean gum-based silver nanocomposite hydrogels: Preparation, characterization and drug delivery applications

This chapter focuses on the preparation of LBG-based nanocomposite hydrogels along with the corresponding pristine gels, characterization and evaluation of their efficiencies for the oral delivery of anticancer drugs for cancer treatment. The chapter is divided into two sections.

In **Section A** of this chapter, the preparation and characterization of the nanocomposite hydrogel containing LBG, AcM and SNPs, as well as the corresponding pristine hydrogel (**Scheme 5**) and their utilities for the oral delivery of 5-FU have been discussed.

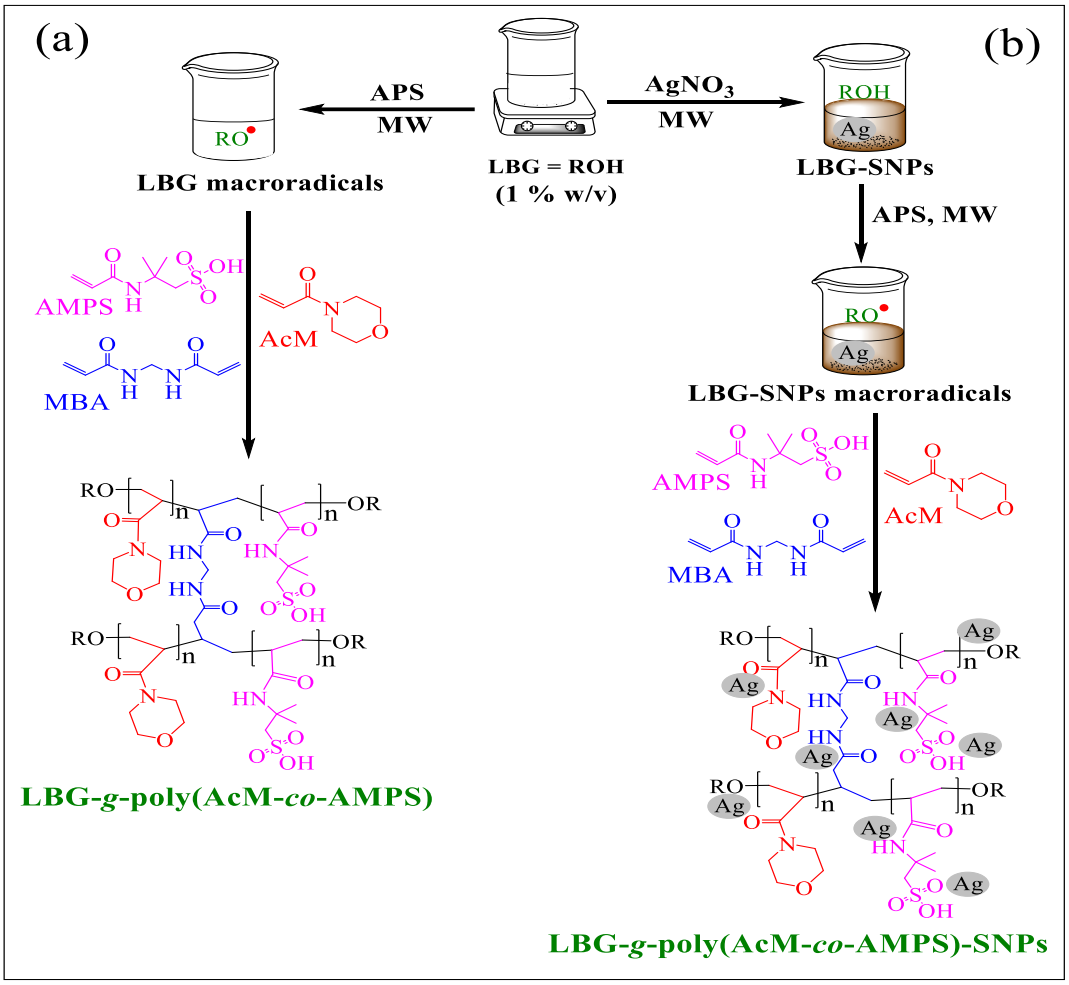


Scheme 5: Mechanism of formation of the (a) pristine gel LBG-*g*-PAcM and (b) nanocomposite LBG-*g*-PAcM-SNPs

The matrices showed higher swelling and drug release at pH 1.2 (SGF) than at pH 7.4 (SIF). The data obtained at pH 1.2 was found to best fit with the first-order kinetic and Korsmeyer-Peppas models. The transport of the incorporated 5-FU from the polymer matrices to the

dissolution medium corresponded to a Fickian diffusion mechanism. The results of the cytotoxicity study towards IEC-6 cells proved the cytocompatibility of the prepared nanocomposite towards normal cells.

In **Section B** of this chapter, the preparation and characterization of the nanocomposite hydrogel containing LBG, AcM, AMPS and SNPs, as well as corresponding pristine hydrogel (**Scheme 6)** and their applicabilities for oral co-delivery of CPT and DOX have been discussed.



Scheme 6: Mechanism of formation of (a) pristine gel LBG-*g*-poly(AcM-*co*-AMPS) and (b) nanocomposite LBG-*g*-poly(AcM-*co*-AMPS)-SNPs

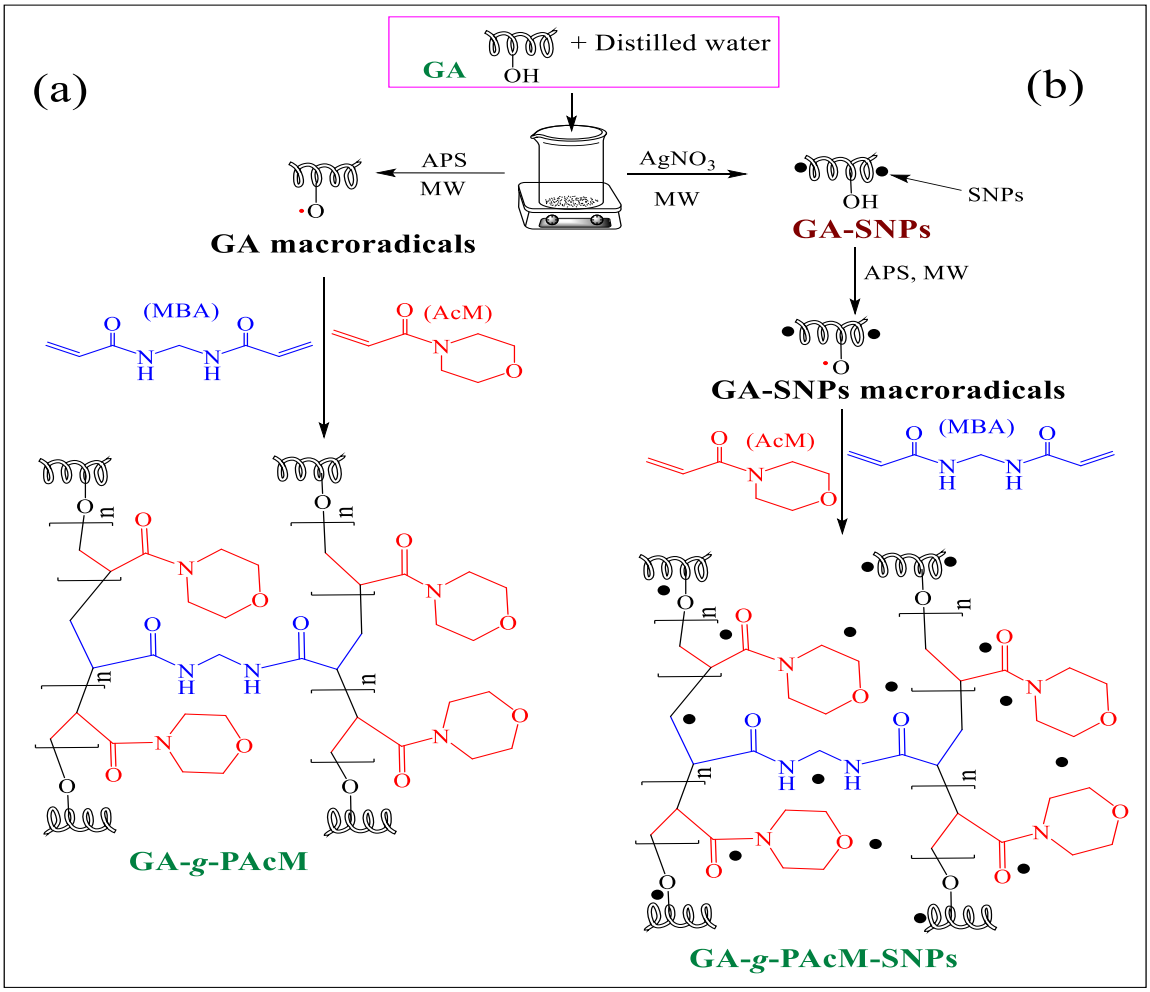
The matrices showed higher swelling and drug release at pH 7.4 (SIF) than at pH 1.2 (SGF). The drug release data at pH 7.4 adhered to the first-order kinetic and Korsmeyer-Peppas models. The transportation of the incorporated drugs from the polymer matrices to the dissolution medium corresponded to a non-Fickian diffusion for CPT and Fickian diffusion for DOX. The

cytotoxicity study of MCF-10A cells revealed that the prepared nanocomposite is cytocompatible and suitable for the oral delivery of CPT and DOX in the gastrointestinal tract.

Chapter-6: Gum arabic-based silver nanocomposite hydrogels: Preparation, characterization and drug delivery applications

In this chapter, GA-based nanocomposite hydrogel and the corresponding pristine gel have been studied to evaluate their efficiencies in delivering anticancer drugs for combating cancer. The chapter is divided into two sections.

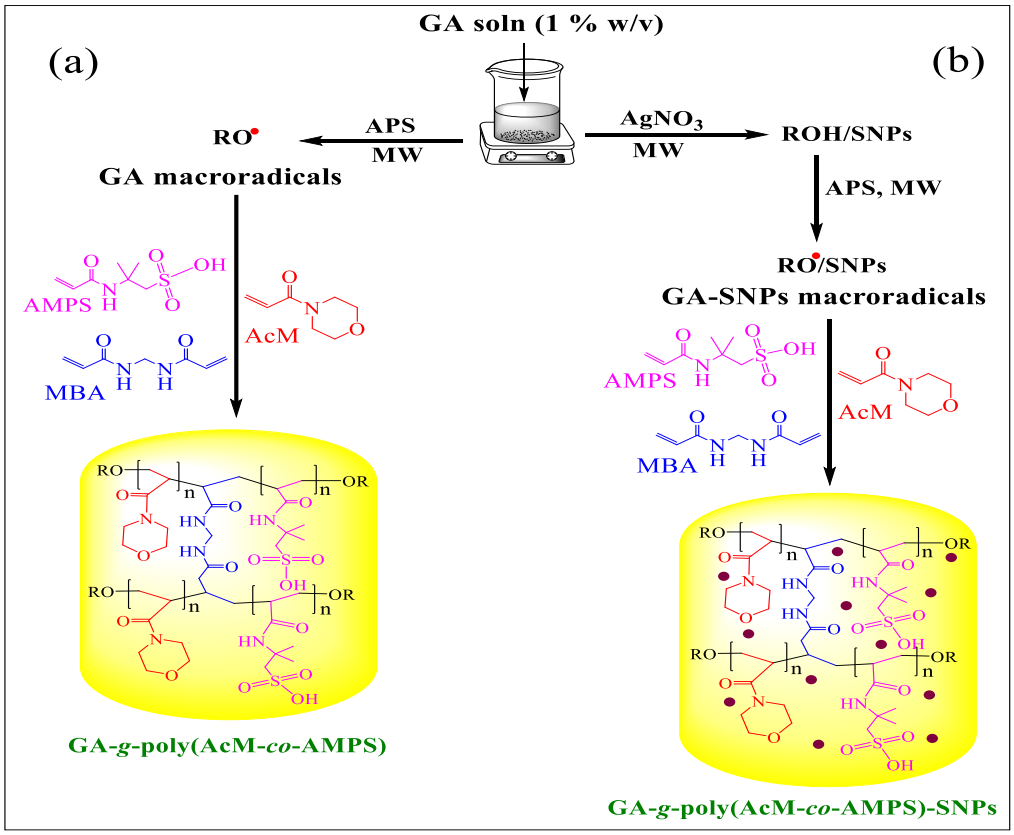
In **Section A** of this chapter, the preparation and characterization of the nanocomposite hydrogel containing GA, AcM and SNPs, as well as corresponding pristine hydrogel (**Scheme 7**) and their utilities for the oral co-delivery of CUR and CPT have been discussed.



Scheme 7: Mechanism of formation of the (a) pristine gel GA-*g*-PAcM and (b) nanocomposite GA-*g*-PAcM-SNPs

The matrices showed pH-responsive swelling and drug release profiles. Higher swelling was observed at pH 7.4 than at pH 1.2, which agreed with the drug release profile. In comparison with the pristine gel, nanocomposite exhibited higher swelling and release efficiencies influenced by the embedded SNPs. The incorporated drugs were released in a sustained manner in all release conditions, with higher drug release at pH 7.4 (SIF) than at pH 1.2 (SGF). The drug release data obtained at pH 7.4 obeyed the first-order kinetic and Higuchi square root models. The transport of the two incorporated drugs from the polymer matrices to the dissolution medium corresponded to a non-Fickian diffusion mechanism. The developed nanocomposite exhibited significant viability towards MCF-10A cells, indicating its cytocompatibility, promising its use for the oral co-delivery of CPT and CUR.

In **Section B** of this chapter, the nanocomposite hydrogel containing GA, AcM, AMPS and SNPs and its corresponding pristine hydrogel (**Scheme 8**) and utilities for the co-delivery of CUR and DOX have been discussed.



Scheme 8: Mechanism of formation of the (a) pristine gel GA-*g*-poly(AcM-*co*-AMPS) and (b) nanocomposite GA-*g*-poly(AcM-*co*-AMPS)-SNPs

The swelling and drug release studies reveal the pH-responsiveness of the developed polymer matrices. Based on swelling and drug release data, the nanocomposite displayed higher swelling and release efficiencies than the corresponding pristine gel attributed to the presence of SNPs. The time-dependent sustained release of the loaded drugs was observed, with higher release at pH 7.4 (SIF) than at pH 1.2 (SGF). The drug release data obtained at pH 7.4 was best fitted to the first-order kinetic and Korsmeyer-Peppas models. The transport of the two incorporated drugs from the polymer matrices to the dissolution medium corresponded to a non-Fickian diffusion mechanism. A higher survival rate of healthy MCF-10A cells was observed in the presence of both blank and drug loaded nanocomposites, which proved that the developed nanocomposite is cytocompatible and suitable polymer matrix for the oral co-delivery of CUR and DOX.

Summary and Conclusions

The results of the whole study have been summarized and the conclusions drawn are presented in this section. In particular, the influence of the hydrophilic and hydrophobic functional groups of both, the polymer matrices and the drugs, on the efficiency of the materials to entrap and release drugs is highlighted. The drug release profiles of all prepared polymer matrices aligned with the corresponding swelling behavior. The release of the drugs from the polymer matrices to the dissolution medium depended on the pH of the release medium, the composition of the polymer matrices and the nature of the drugs. The kinetics and mechanism of the drug release varied based on the nature of the polymer matrices and the incorporated drug. All polymer matrices studied exhibited significant cell viability, indicating the possibility of using these nanocomposite hydrogels for the oral delivery of anticancer drugs in both single and combined forms for cancer treatment. The comparative drug release efficiencies of the developed polymer matrix materials with the similar studies reported previously and the future scope of the work have been provided in this section. Bibliographic references for the work cited in the text have been provided at the end of each chapter.

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